REMARKS

Claims 1-56 were pending in this application. Claims 1-27 and 31-48 have been withdrawn from consideration as being drawn to a non-elected invention. Previously presented claims 51-54 have been canceled without prejudice or disclaimer. New claims 57-61 have been added for consideration. Support for the new claims can be found throughout the specification and in particular, on page 7, lines 30-33; on page 28, lines 4-15; on page 32, lines 1-7; on page 40, lines 23-32 on to page 41, lines 0-3; on page 71, lines 20-24; on page 73, lines 0-2; on page 74, lines 9-14 and on page 75, lines 10-26. Support for the amendment to claim 28 can be found throughout the specification, and particularly on page 24, lines 6-30; on page 29, lines 26-32 continuing on to page 30, lines 0-10; and in Example 5, pages 53-56. Thus, as a result of the foregoing amendments, claims 28-30, claims 49-50 and 55-56, which were previously presented, and new claims 57-61 are under consideration. No new matter has been entered by way of this amendment.

By way of the present communication, the Examiner alleges that amended claim 28 and new claims 50-56 are directed to an invention that is independent or distinct from the originally claimed invention. While Applicants respectfully traverse the Examiner's rejection of the amended and new claims submitted in the response to the Office Action mailed April 14, 2004, Applicants include herein for consideration a newly amended claim 28 and new claims that Applicants believe fall within the scope of the claims as originally filed and elected by way of the restriction requirement, and for which there is support in the application as filed. In addition, for convenience and clarity, Applicants have also repeated below the response to the objections raised in the previous Office Action, dated April 14, 2004.

Applicants' representatives would like to express their sincere appreciation for the telephonic discussion held with Examiner Gary Nickol on October 19, 2004 as related to the Office Communication mailed October 4, 2004. As noted in that conversation, Examiner Nickol provided an explanation as to why the Office Communication was forwarded and kindly noted that Applicants may call him in the future to address any further related issues after the response is filed.

In the Office Action mailed April 14, 2004, the Examiner objected to the specification since the specification on page 1 does not reflect the priority status of the present application. Applicants have amended the specification as suggested by the Examiner in the response filed to that Office Action on July 14, 2004, and repeated herein for convenience. Accordingly, withdrawal of the objection is respectfully requested.

The Examiner also alleged in the Office Action mailed April 14, 2004, that no IDS had been filed in the present application and that the previously filed and signed IDS, submitted with the filing of the present application, was not considered in this application. Applicants respectfully pointed out to the Examiner that the MPEP states in Chapter 600, under 609 I.A.2. Continuation Applications or Divisional Applications Filed under 37 CFR 1.53(b)....that:

" The Examiner will consider information which has been considered by the Office in a parent application when examining (A) a continuation application filed under 37 CFR 1.53(b) or filed under former 37 CFR 1.60, (B) a divisional application filed under 37 CFR 1.53(b) or filed under former 37 CFR 1.60, or (C) a continuation-in-part application filed under 37 CFR 1.53(b). Such information need not be resubmitted in the continuing application unless the applicant desires the information to be printed on the patent."

Accordingly, Applicants requested consideration of the references submitted in the IDS filed with the parent application, to which the present application claims priority.

In the Office Action dated April 14, 2004, the Examiner had rejected claims 28-30 under 35 U.S.C. 102(b) as being anticipated by Engleman et al. (WO 94/02156). Applicants have amended the claims and provided arguments as to the differences between the claims as amended and the reference cited. Applicants assert that the claims as currently pending do not read on the subject matter of Engleman et al. Withdrawal of the rejection is respectfully requested.

Objections to the Specification

The Examiner had previously objected to the specification for the following reason: The specification on page 1 should be amended to reflect the priority status of the

present application. Applicants have amended the specification as requested by the Examiner, and as such, withdrawal of the objection is respectfully requested.

Information Disclosure Statement

As noted above, the Examiner alleged that no IDS was submitted for consideration in the present application. Applicants respectfully asserted that upon filing the present continuation application, the IDS that was submitted with the parent application, USSN 09/251,896, now U.S. patent 6,602,709, was also submitted for consideration in the present application. Applicants respectfully requested entry of the previously filed IDS for consideration in the present application.

Rejections under 35 USC 102(b)

The Examiner has rejected claims 28-30 under 35 U.S.C. 102(b) as being anticipated by Engleman et al. (WO 94/02156). Applicants respectfully traverse the Examiner's rejection, and have amended claim number 28 to better clarify what Applicants believe to be the invention. Support for the amendment can be found throughout the specification, and particularly on page 24, lines 6-30; on page 29, lines 26-32 continuing on to page 30, lines 0-10; and in Example 5 on pages 53-56. Further support for the enablement of this subject matter can be found on page 49, lines 19-32, and in Figure 5.

The Examiner alleges that Engleman et al. teach a method of assessing cytotoxic T lymphocyte activity comprising contacting antigen presenting dendritic cells with a variety of antigen donors including bacterial, parasitic, fungal, viral, and tumor antigens. The antigens may be purified, recombinant, or exist as whole organisms or cells in viable or dead form. The Examiner further alleges that the reference teaches exposing antigen presenting dendritic cells to a population of T lymphocytes to be assayed for their ability to exhibit killer cell activity and assaying the cytotoxic activity of the T lymphocytes exposed to the antigen presenting DCs. The Examiner further alleges that although the reference does not specifically teach contacting the dendritic cells with "apoptotic cells", Engleman et al. teach that pulsing DCs includes contact with irradiated cells.

Applicants respectfully traverse the Examiner's rejection and assert that in order for a rejection under 35 U.S.C. 102(b) to be proper, the reference(s) must recite each and every element of the invention as claimed. Applicants assert that Engleman et al. do not

teach the methods of the present invention as currently claimed and that there are distinct differences between the teachings of Engleman et al. and the present application.

For example, claim 28, as currently amended recites:

".....providing antigen presenting dendritic cells prepared by

contacting dendritic cells with apoptotic cells expressing an antigen or apoptotic cell fragments, blebs, or bodies containing antigen...."

It is apparent that Engleman et al. did not appreciate the complexity of the methods necessary for inducing or assessing cytotoxic T lymphocyte killing activity by delivering antigen by way of an apoptotic cell. In fact, it was only through the work of the present inventors that such unexpected findings became apparent. For example, as disclosed in the instant application, dendritic cells are noted in the present application as having the ability to efficiently phagocytose apoptotic cells expressing the desired antigen or apoptotic cell fragments, blebs, or bodies containing antigen, and presenting them in the context of HLA antigens for efficient induction of T cell responses.

Applicants respectfully point out to the Examiner that Engleman et al **did not** contemplate the use of **apoptotic cells or apoptotic cell fragments, blebs, or bodies containing antigen** for delivery to dendritic cells for priming T cells. Engleman et al. did not appreciate the more efficient uptake of antigen by dendritic cells in the context of an apoptotic cell, as shown in the instant application. Moreover, Applicants assert that the irradiation referred to in Engleman et al. was in all likelihood gamma irradiation, which was standardly used by those skilled in the art to render tumor cells replication incompetent prior to use as a vaccine. Such cells would not be as efficient as apoptotic cells in presenting antigen for uptake by dendritic cells, as noted in the instant application. Moreover, Applicants assert that the reference of Engleman et al is not enabled for methods of inducing apoptosis using the irradiation procedures as noted in the present application.

For example, on page 31, lines 19-27, it is noted that:

"Those skilled in the art will recognize that optimal timing for apoptosis will vary depending on the donor cells and the technique employed for inducing apoptosis. Cell death can be assayed by a variety of methods known in the art including, but not limited to, fluorescence staining of early markers for apoptosis, and determination of percent

apoptotic cells by standard cell sorting techniques."

Furthermore:

"In one embodiment, donor cells are induced to undergo apoptosis by irradiation with ultraviolet light. Depending on the cell type, typically exposure to UV light (60 mjules/cm^2/sec) for 1 to 10 minutes induces apoptosis. This technique can be applied to any cell type, and may be most suitable for a wide range of therapeutic applications. The apoptotic donor cells expressing an antigen of interest on their surface could then be used to prime dendritic cells in vitro or in vivo."

More particularly, the methods of inducing apoptosis by UVB irradiation, as shown by the inventors of the instant application, can be found on page 21, lines 0-3, wherein it states:

"HeLa cells were labeled with PKH26-GL, followed by irradiation using a 60UVB lamp [Derma Control Inc.], calibrated to provide 240 mJ cm^{-2} in 2 minutes, sufficient for the induction of apoptosis."

Furthermore, the instant application points out specific and relevant differences in necrotic cells as compared to apoptotic cells as related to their use for either antigen presentation or maturation of the dendritic cell. It is Applicants' contention that Engleman et al. did not appreciate the difference between use of either an apoptotic cell or a necrotic cell for purposes of inducing or assessing a T cell response. Nor could Engleman et al. appreciate these differences in outcome of responses until the time of the present invention.

With respect to the claim amendments, the Examiner's attention is drawn to page 4, line 32, continuing on to page 5, lines 0-2:

"It is also contemplated by this invention that the dendritic cells can be exposed to a preparation of donor apoptotic cell fragments, blebs or bodies rather than whole apoptotic cells."

Applicants further assert that Engleman et al. did not contemplate that donor cells could be transfected with the gene encoding the desired antigen prior to induction of apoptosis for efficient delivery to dendritic cells, which would then present the antigen to T cells in the context of HLA antigens. For example, in the instant application on page 5, lines 3-9:

"In another embodiment of this invention, the donor cells can be transfected, transduced or transformed to express foreign antigens prior to induction of apoptosis. A variety of such antigens may be expressed by the donor cells including, but not limited to, viral antigens, tumor antigens, toxins, microbial antigens, and autoimmune antigens."

And yet further, on page 5, lines 10-21:

"Accordingly, this invention also provides a method of generating antigen-specific cytotoxic T lymphocytes comprising providing a population of apoptotic cells, or membrane containing fragments thereof, expressing said antigen, exposing dendritic cells to said apoptotic cells for a time sufficient to allow said antigen to be internalized and processed by the dendritic cells, and exposing T lymphocytes in vivo to said dendritic cells for a time sufficient to induce said lymphocytes to become antigen-specific T lymphocytes. This invention further contemplates induction of antigen-specific T lymphocytes in vitro."

With respect to new claim numbers 59 and 60, the Examiner's attention is drawn to page 71, lines 20-24 which provides support for these claims, wherein it states:

"Immature DCs efficiently phagocytose apoptotic cells. Based on previous observations that immature DCs are the cells responsible for capturing antigen (106), we predicted that apoptotic cells would be engulfed best by immature DCs."

Further support can be found on page 73, lines 0-2, where it states:

"This data also demonstrates that it is the immature DC which preferentially acquires apoptotic material as compared to the mature DC."

And yet further support is found on page 74, lines 9-14:

"While mature DCs were efficient targets when infected with influenza, they were unable to cross-present antigens, presumably because they had down regulated the ability to phagocytose the apoptotic monocytes. The immature DCs, however, did cross-present antigens from apoptotic cells."

And yet further support can be found on page 75, lines 10-26:

"Immature DCs can be distinguished from macrophages by intracellular expression of CD83 and a unique profile of phagocytic receptors. We investigated the possibility that immature DCs might phagocytose apoptotic cells via pathways distinct from macrophages. To clearly distinguish these cells we characterized them

phenotypically. Immature DCs are distinguished by the absence of both CD14, a macrophage restricted marker, and CD83, a maturation marker for DCs (125). We have extended the use of CD83, finding that immature DCs can be distinguished from both macrophages and mature DCs by their intracellular expression of CD83 [FIG. 18]. Macrophages do not express CD83 intracellularly nor extracellularly [FIG. 18], while mature DCs express CD83 both intracellularly and extracellularly [FIG. 18]."

Support for new claim 61 can be found on page 28, lines 4-15, wherein it states:

"Apoptotic cells may be used to deliver antigen to either immature or mature dendritic cells, either freshly isolated or obtained from in vitro culture. In a preferred embodiment, apoptotic cells comprising an antigen are co-cultured with immature dendritic cells for a time sufficient to allow the antigen to be internalized by the immature dendritic cells. These immature dendritic cells are then caused to mature by the addition of a maturation factor to the culture medium. The matured dendritic cells expressing processed antigen on their surface are then exposed to T cells for potent CTL induction."

Accordingly, Engleman et al. do not contemplate nor appreciate the need for antigen uptake and transfer to the dendritic cell by way of an apoptotic cell, which is then presented to the T cell in the context of the MHC. Applicants further assert that the Engleman et al publication **does not teach or suggest** the preparation and use of antigen containing apoptotic cells to dendritic cells for induction or assessment of T cell activity. Nor do Engleman et al. teach how to prepare apoptotic cells containing the antigen for delivery to the dendritic cell. In fact, the only antigens taught by Engleman et al are KLH, SWM and HIV antigens, **which are not presented in the context of an apoptotic cell**. Applicants assert that the rejection under 35 U.S.C. § 102(b) is improper in that the Engleman et al reference is a non-enabling reference. As stated in In re Donohue, 766 F.2d 531, 533, 226 USPQ 619, 621 (Fed. Cir. 1985):

> It is well settled that prior art under 35 U.S.C. § 102(b) must sufficiently describe the claimed invention to have placed the public in possession of it. Accordingly, even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling. It is not, however, necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement.

Applicants further assert that **the use of apoptotic cells as an entity capable of transferring antigen to dendritic cells was unknown prior to Applicants' own work**. Applicants further assert that the use of apoptotic cells to transfer antigen to dendritic cells to charge MHC I for the priming of CD8 positive T cells was also unknown prior to Applicants' own work. Thus, Engleman et al **do not** teach the art of priming T cells or assessing T cell activity using dendritic cells exposed to antigen delivered via apoptotic cells. It was only at the time of the present invention that such an unexpected finding became apparent.

Thus, Engleman et al. **do not disclose nor suggest use of apoptotic cells expressing antigen or apoptotic cell fragments, blebs, or bodies containing antigen** for delivery to dendritic cells for induction of or assessment of T cell activity.

It is Applicants contention that Examiner has tried to reconstruct Applicants' invention using hindsight reconstruction, which is impermissible.

In light of the foregoing claim amendments and arguments, Applicants respectfully request withdrawal of the rejection.

Fees

No fees are believed to be due for the present response. However, should this be in error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or to credit any overpayments.

Conclusion

Applicants believe that the foregoing amendments to the claims place the application in condition for allowance. Withdrawal of the rejections and objections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 118, to effect a resolution.

Respectfully submitted,

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